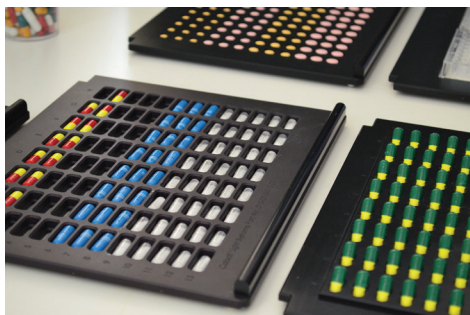


# Quantification of Tablets Containing Multiple APIs Using Transmission Raman Spectroscopy



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## Abstract

The ability to predict multiple constituents of a final dosage form in one fast, nondestructive measurement can reduce analysis time and cost significantly. This is especially beneficial when quantification of multiple active pharmaceutical ingredients (APIs) is required for tests such as content uniformity, assay, and identity (ID). This example, based on a common cold and flu product, demonstrates the quantification of five components (three APIs and two excipients) with a nine-second measurement. Nominal concentrations for the APIs ranged from 1 to 85 % w/w.

## Introduction

Typical solid dose forms of a drug product contain at least one active pharmaceutical ingredient (API) and a range of excipients at varying levels. The most widely used means of quantitative analysis is high-performance liquid chromatography (HPLC), which is often the standard reference technique. HPLC is highly capable; however, sample preparation is resource intensive, consumables are needed and analysis takes time to complete. This formulation requires a different separation step and analytical test for the phenylephrine component, and HPLC is not commonly used for excipient analysis. Transmission Raman spectroscopy (TRS) is a regulatory-acceptable alternative technique for content uniformity, assay, and drug product identity, enabling fast, nondestructive analysis of tablets and capsules without chemical preparation or skilled analytical chemists.

Usually, only APIs are quantified, but monitoring excipients as well as APIs may be advantageous. For example, if a particular batch of drug product differs in terms of one of its excipients, it may affect one of the quality critical attributes, such as dissolution. This extra information comes with almost no extra cost or complexity from transmission Raman methods.

## Experimental

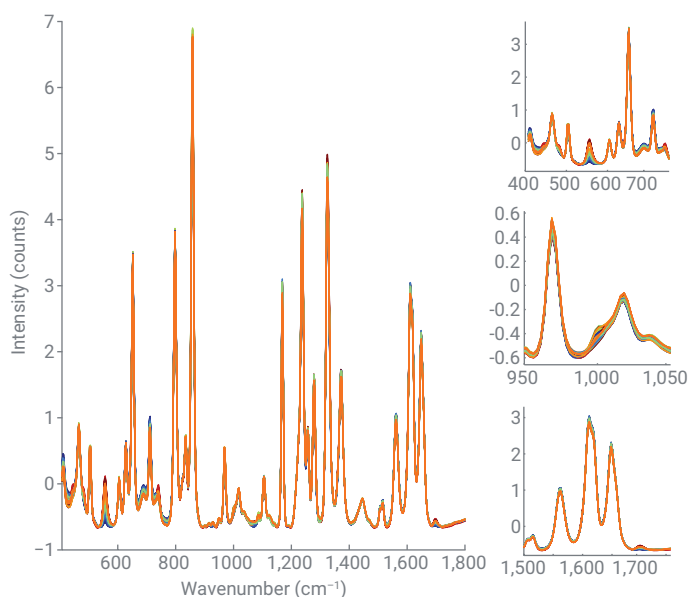
The drug product in this example, a common cold and flu formulation, contained five constituents (three APIs and two excipients) at the nominal concentrations shown in Table 1. This product is expensive to analyze by HPLC and gas chromatography instruments, and takes several days to complete.

Using TRS to quantify multiple components requires a thorough calibration set. The calibration design in this example included an orthogonal five-level design consisting of 20 samples. To validate the models, five independent validation samples with varying concentrations were tested.

Powdered materials were weighed, ground, mixed, and compressed into tablets. Samples were loaded into a sample tray, then into the Agilent TRS100 Raman system for automated analysis. Two tablets per sample were scanned using 1.0 W laser power (830 nm) for nine seconds. The spectra shown in Figure 1 indicate the regions of variation due to constituents.

**Table 1.** Cold and flu formulation.

Component	Percent
Phenylephrine	1 %
Caffeine	4 %
Paracetamol	85 %
Magnesium stearate	1 %
Tabletose	9 %



**Figure 1.** Calibration spectra, baselined and normalized to show spectrum variation.

## Results and Discussion

Calibration spectra were used to build predictive models for each constituent of the mixture (Figure 2).

The results indicate that PLS models can be built for all constituents, with good model parameters for the APIs. Of all the constituents, magnesium stearate was the worst performing model. This was due to the poor Raman scattering ability of the constituent and the low concentration,

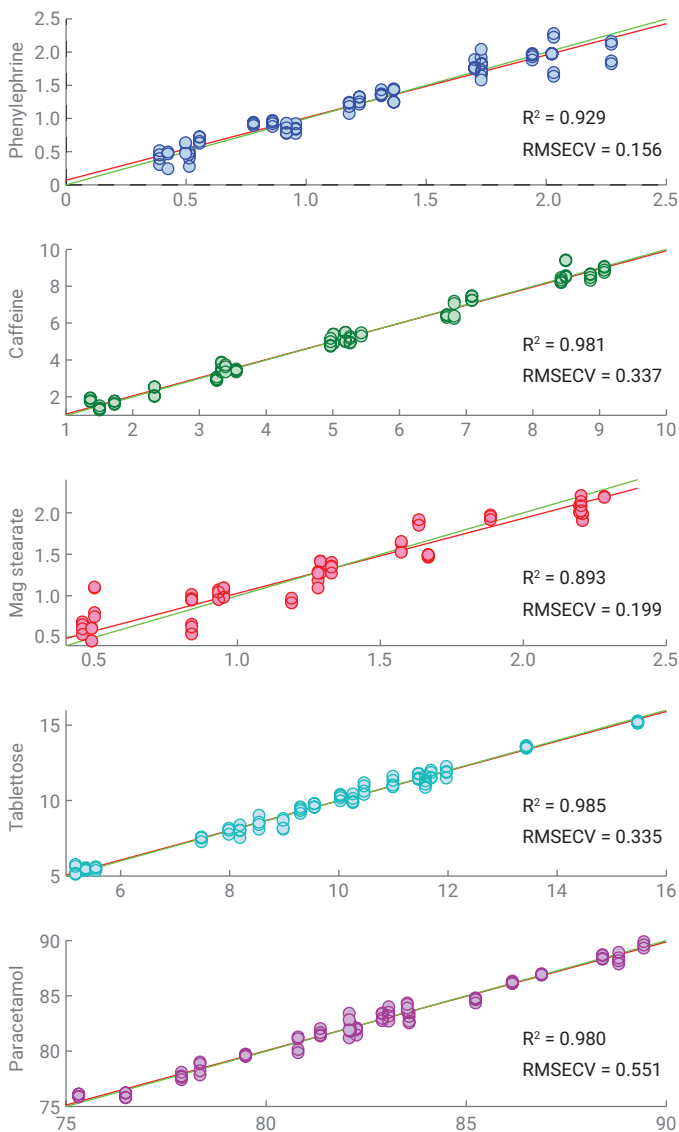


Figure 2. PLS Calibration models and statistics for each constituent.

at 1 % w/w. Of greatest importance is the success of the phenylephrine model, which gives acceptable model performance in a single measurement, even though the spectra are dominated by the acetaminophen component.

Figure 3 shows the validation of the model, and prediction of independent samples. Results indicate that all substances were predicted well, with higher performance for the stronger Raman scatterers (the APIs and caffeine, as the highest content excipient).

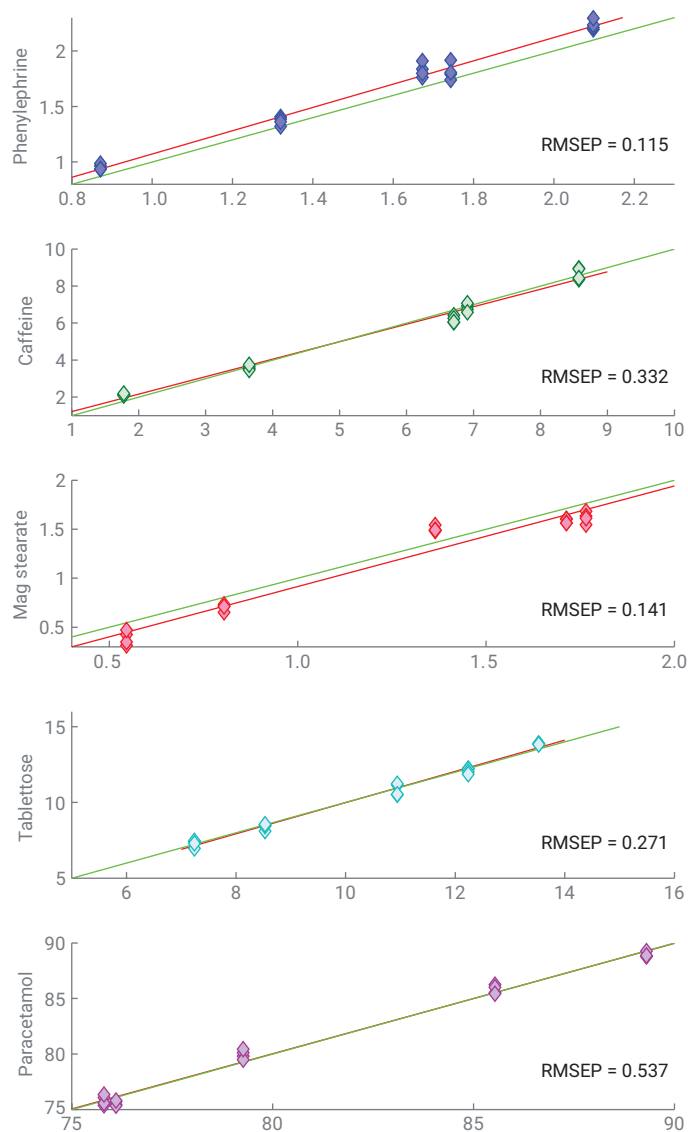


Figure 3. PLS Validation results for each constituent.

## Conclusions

This Application Note demonstrates that multiple APIs in a single intact tablet can be quantified easily by TRS. The time taken for content uniformity, assay, and identity was reduced from approximately two days (by chromatographic methods) to less than five minutes for a batch of 10 tablets, and does not require skilled analytical resources for routine testing.

With little extra effort, the concentrations of excipients are also determined in the method, which can provide useful attributes for process monitoring applications.

TRS is an effective and powerful tool for quantifying multiple APIs quickly and effectively, even for low-concentration components.

## Reference

1. J. Griffen, A. Owen, P. Matousek. Comprehensive quantification of tablets with multiple active pharmaceutical ingredients using transmission Raman spectroscopy – A proof of concept study. *Journal of Pharmaceutical and Biomedical Analysis* **2015**, 115, 227–282.

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